HTAi Workshop
A Primer on RICC: How to Generate Real World Evidence? A Modern Approach

Friday 1 June 2018, 8:30-12:00
Cypress 2, Level 2, Westin Bayshore Hotel

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Chair, Regulatory Interactions and Conditional Coverage IG, HTAi
A paradigm change has just happened!

Disease oriented care
- EBM
- Clinical trials

Patient oriented care
- RWE
- Observational studies

Interest over time charts for clinical trial, evidence based medicine, observational study, and real world evidence.
Increasing focus on RWE is associated with the greater supply of electronic patient-level data.

Cumulative publications; some of the research output is not related to medicines
Source: PubMed
The volume of « unused » data is massively growing.

Source: IDC Digital Universe Study
RWD supply push may cause a seismic shift in the way we evaluate medicines.

**THE PAST**

**RCT**
Controlled trials, manufacturer led

**Few**
Few evaluators at launch, mostly regulators and large payers

**Efficacy and Safety**
Initial view of benefit-risk

**THE PRESENT**

**RCT and RWE**
Shift to secondary patient-level data across

**Many**
Many groups over time including clinical and small payers

**Almost everything**
Insights on environment, outcomes, costs, comparative effectiveness
Generating evidence from real world data (RWD)

Data sources

- Consumer data
- Social media
- Claims databases
- Test results, lab values, pathology results
- Hospital visits, service details
- Pharmacy data
- Electronic medical and health records
- Mortality, other registries
- Primary data collection (excluding RCTs)

Meaningful questions

Fit for purpose data

Appropriate Analyses

REAL-WORLD EVIDENCE (RWE)
### Step 1: Asking the right questions

<table>
<thead>
<tr>
<th>Regulatory</th>
<th>HTA</th>
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<tbody>
<tr>
<td>Exposure</td>
<td>Burden of target disease (mortality, morbidity prevalence, incidence, DALYs, QALYs)</td>
</tr>
<tr>
<td>Epidemiology of the indication(s)</td>
<td>Conditions of use</td>
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<tr>
<td>Prescribing conditions</td>
<td>Expected benefit of the technology</td>
</tr>
<tr>
<td>Characteristics of patients who actually receive the drug</td>
<td>- On burden of disease</td>
</tr>
<tr>
<td>New safety concerns, known ones, risk factors</td>
<td>- On management of disease</td>
</tr>
<tr>
<td><strong>Efficacy</strong> in real life / in specific populations</td>
<td>- Economical</td>
</tr>
<tr>
<td><strong>Effectiveness</strong> of risk minimization measures</td>
<td>- Organisational</td>
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<tr>
<td>Signal detection</td>
<td>- Social</td>
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**Confirmation of the expected benefit versus risk**

**Potential to cover unmet medical needs or to improve covered needs**
Step 2: Finding fit-for-purpose data

- Relevance (appropriate data)
- Accuracy (less errors)
- Timeliness (data still useful)
- Linkability (identifying fields)
- Completeness (less missing records / variables)
- Accessibility (available easily)
- Representativeness
Cost effective approach to data collection

The data shall be collected entirely (primary)

The data shall be collected partially (enriched, mosaic)

The data resides in a database (secondary)

We don't know if the data is available in a database (landscaping)

Begin with the research question.

Relevance

Cost

Time

Design freedom
Claims data

Initial purpose
- Economic management
- Reimbursement

Content
- Demographics
- Diagnoses
- Diagnostic related groups
- Procedures
- Reimbursed drugs/devices

Settings
- Mainly Hospitals
- Increasingly linked to outpatient claims

Good for
- Economic and resource utilization
- Epidemiology
- Healthcare system
EMR data

**Initial purpose**
- Clinical management
- Patient follow up

**Content**
- Demographics
- Diagnoses
- Signs and symptoms, allergies, smoking
- Lab values
- Drugs and to a less extent procedures

**Settings**
- Mainly primary care
- Increasingly secondary care and hospitals

**Good for**
- Exposure evaluation
- Drug utilization
- Disease epidemiology
- Benefit-risk assessment
- Unmet needs, burden, adherence
Pharmacy records / sales data

**Initial purpose**
- Sales management
- Benchmarking

**Content**
- Demographics
- Drugs (packages sold)

**Settings**
- Retail pharmacies
- Wholesales
- Company outputs

**Good for**
- Exposure
- Treatment dynamics (switch, discontinuation…)
- Population movements
- Linkage
Registries

Initial purpose
• Research

Content
• Demographics
• Clinical details
• Procedures
• Drugs
• Lab values
• Relevant markers, genetic data, tests, etc

Settings
• Disease or drug oriented
• Mostly secondary care
• Mostly research intensive areas (oncology, ...)

Good for
• Disease epidemiology
• Benefit-risk assessment
• Treatment pathways
Social media, wearables, connected devices, etc

**Initial purpose**
- Networking
- Follow up
- Experimental

**Content**
- Demographics
- Narrow and specific data

**Settings**
- Everyday life
- Smoothly entering the healthcare system
- Telemedicine programs

**Good for**
- Hypothesis generation
- Signal detection / monitoring
- Population behavior
- Public health intervention evaluation
Syndicated surveys

Initial purpose

- Market Research

Content

- Demographics
- Clinical data
- Procedures
- Labs & specialized tests
- Drugs
- Outcome measures

Settings

- Inpatient & outpatient
- Focused on pathologies with high demand for data

Good for

- Disease epidemiology
- Treatment dynamics (split per indication, off label use,...)
- Clinician behavior and understanding
Linking different types of secondary data may be needed.

- National claims, dispensing data
- Electronic Medical Records
- Labs, registries, biobanks

T-Shaped model for better efficiency in database studies

Deep, flexible therapy area specific data including primary data collection

Range of data types

Broad

Deep
Step 3: Conducting the appropriate analyses

**BETTER TRADITIONAL STUDIES**

Improved *execution* of traditional studies, more *precise selection* of sites, reduced timelines and errors

**INNOVATIVE STUDY DESIGN**

Collect data from clinicians and/or directly from patients; combine with existing data for broader stakeholder value

**SMARTER EVIDENCE GENERATION**

Reusable, scalable approaches to evidence generation
Data and technology make innovative designs possible

Traditional

Primary data collection

Secondary data collection

New

Pragmatic clinical trials
Prospective research (registries, RCTs)
Extension studies with direct to patient follow-up
Mosaic studies & Enriched studies
Site less studies
Augmentation studies
Database studies
Evidence platforms

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Mosaic studies identify the best-fit data in each country

**What are Mosaic studies?**

- Due to the differences in secondary data availability across countries, one method for data collection cannot be always used in all countries
- Mosaic studies use multiple data collection approaches within a single study - countries are grouped according to the method for data collection— to provide an optimised study design to the client.

**Case Study: A Global PASS**

**Challenge:**
- Client wanted a cost effective and innovative solution for a PASS in US and EU (~5000 patients globally over 10 year time-frame)

**Enriched opportunity:**
- Bring together a segmented solution for the best-fit design for the US and each EU market, identified by the use of secondary data for feasibility and planning
- Use data from claims + primary site network to identify optimal US sites for recruitment & data collection
- Utilize network of registries to collect, analyse and pool relevant safety information

**Enriched value points:**
- Huge cost efficiencies (~$25M) through avoidance of unnecessary data collection in certain markets
- Early indication of improved site and patient recruitment timelines using IQVIA data–driven approach
Enriched studies combine primary and secondary data

**EMR “backbone”**
- Aids patient recruitment
- Provides core patient information

**STUDY DATABASE**
- Linkage and de-ID patient information
- Final study database linking all data sources

**EMR data**
- Other datasets (e.g. claims)

**STUDY PLANNING**
- E-CRF and PRO provide supplementary data on variables not in EMR, including QoL

**RECRUITMENT**
- Data collected directly from MD (e-CRF)

**STUDY EXECUTION**
- Patient reported outcomes (PRO)
Evidence platforms: the future of evidence generation

• **Evidence platforms** are built on a foundation of real world data that supports clinical and commercial needs.

• It embeds a layer of technology to extract and analyze the data in a consistent way across the organization, with appropriate governance and privacy protections.

• Applications designed to help teams use those insights appropriately for their needs.
Trends in real-world data, evidence, and insights

Expanding application of RWD in clinical development

Increasing use and acceptance of innovative study designs to generate RWE

Scalable approaches to generate real world insights (RWI)
Thank you!

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• Real World Analytics Solutions (RWAS)
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Many types of data sources can be used in an Enriched study:

- **Electronic Medical Records**
  - Completed by physicians during routine practice; Mainly containing primary care data

- **Electronic Case Report Forms**
  - Completed by physicians/delegates during studies; Containing information collected as per protocol

- **Patient Reported Outcomes**
  - Completed by patients enrolled in the study; Containing information about the patients’ Quality of Life collected as per protocol / routine practice

- **Claims data**
  - Completed by physicians during routine practice; containing information about healthcare utilisation

- **Registries**
  - Collected by physicians during routine care; Containing not only data about patients’ medical history but also data about hospitalisation and drugs dispensed

Data extracted from each source is linked at the **Patient Level** using unique identifiers and combined into one comprehensive data set.
Example: Extend Follow-up after a Clinical Trial

Understanding long-term benefits of treatment through direct-to-patient research

Our Approach
- Direct to patient follow-up for effectiveness (up to 10 yrs)
- Follow both treated and placebo patients
- Consent patients for new study before trial ends
- Single investigative site per country where possible
- Selected clinical validation for events of special interest (MACE)

Our Value
- Roughly 1/3 cost of using RCT framework for follow-up
- Bulk of budget is directed to minimizing loss to follow-up and obtaining validation for potential MACE
Example: RWD Comparator for Single-Arm Trial

Accelerated approval of Bavencio (avelumab) for metastatic Merkel Cell Carcinoma based on a single-arm trial with RW data provided as context

- **BAVENCIO®** the first immunotherapy for metastatic Merkel Cell Carcinoma
- Approved in 2017 under **FDA accelerated approval** based on tumor response and duration of response. Also approved by EMA and PMDA.
- **JAVELIN Merkel 200 trial:** open-label, single-arm, multi-center study
- **External benchmark data requested by regulators for context**

<table>
<thead>
<tr>
<th>AVELUMAB</th>
<th>N = 88</th>
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<tbody>
<tr>
<td>Overall response rate</td>
<td>33%</td>
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</table>
| Median duration of response among 29 responding patients | • 86% > 6 months  
• 45% > 12 months |

<table>
<thead>
<tr>
<th>Natural history control group with chemotherapy</th>
<th>N = 14</th>
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<tbody>
<tr>
<td>Overall response rate</td>
<td>29%</td>
</tr>
<tr>
<td>Median duration of response among 4 responding patients</td>
<td>1.7 months</td>
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Source: [www.accessdata.fda.gov](http://www.accessdata.fda.gov)
Example: Label Expansion for a Medical Device

Direct-to-Patient Device Registry

- Patients identified and enrolled via prescription
- Direct-to-patient recruitment and surveys via clinically-staffed call center
- Outcome assessed by diagnosis in medical billing records of treating clinician

External Control Via Claims

- Comparators identified from health insurance claims
- Claims data used to capture medical history and outcomes
- Outcome assessed by presence of diagnosis in claims data

Patients Matched Via Propensity Score

Study protocol approved by FDA in 2017 after several meetings
Adding RW Data to Enhance ROI for new biologic

Non-interventional study of newly approved biologic to inform insights on:

- Clinical disease activity
- Treatment patterns
- Patient-reported outcomes
- Adverse Events
- Health-related resource utilization & costs

Patients with moderate to severe disease

Who receive newly approved biologic

100 sites

Adjudicated health insurance claims

Clinical data from physician & patient reported outcomes

Baseline
Every 12 weeks
Every 24 weeks (clinical assessment)
5 year